

Accuracy of Echocardiography to Evaluate Pulmonary Vascular and RV Function During Exercise



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ABSTRACT

OBJECTIVES We compared exercise echocardiography and exercise cardiac magnetic resonance imaging with simultaneous invasive pressure registration (ExCMR_{ip}) for the assessment of pulmonary vascular and right ventricular (RV) function.

BACKGROUND Exercise echocardiography may enable early diagnosis of pulmonary vascular disease, but its accuracy is untested.

METHODS Exercise imaging was performed in 61 subjects (19 athletes, 9 healthy nonathletes, 8 healthy BMPR2 [bone morphogenetic protein receptor type II] mutation carriers, 5 patients with new or worsening dyspnea after acute pulmonary embolism, and 20 patients with chronic thromboembolic pulmonary hypertension). Echocardiographic variables included mean pulmonary artery pressure (mPAP) and systolic pulmonary artery pressure (sPAP), cardiac output (CO), RV fractional area change, tricuspid annular systolic excursion, and RV end-systolic pressure-area ratio as a surrogate measure of RV contractile reserve. ExCMR_{ip} provided measurements of CO, RV ejection fraction, mPAP, sPAP, and RV end-systolic pressure-volume ratio at rest and during exercise. Abnormal pulmonary vascular reserve was defined as mPAP/CO slope >3 mm Hg/l/min by ExCMR_{ip}.

RESULTS Echocardiographic determination of mPAP/CO was possible in 53 of 61 subjects (87%). mPAP/CO by echocardiography was higher than that obtained by ExCMR_{ip} (+0.9 mm Hg/l/min; 95% limits of agreement, −3.6 to 5.4), but enabled accurate identification of patients with abnormal pulmonary vascular reserve (area under the receiver-operating characteristic curve, 0.88 [95% confidence interval (CI): 0.77 to 1.00, $p < 0.0001$]). Simplified relationships between sPAP and exercise intensity had similar accuracy in identifying subjects with pulmonary vascular disease (area under the receiver-operating characteristic curve, 0.95 [95% CI: 0.88 to 1.01], $p < 0.0001$). RV fractional area change by echocardiography correlated strongly with RV ejection fraction by ExCMR_{ip}, whereas a moderate correlation was found between tricuspid annular systolic excursion and RV ejection fraction. A moderate correlation was found between ratios of peak exercise to resting RV end-systolic pressure-area ratio and RV end-systolic pressure-volume ratio ($r = 0.64$, $p < 0.0001$).

CONCLUSIONS Echocardiographic estimates of RV and pulmonary vascular function are feasible during exercise and identify pathology with reasonable accuracy. They represent valid screening tools for the identification of pulmonary vascular disease in routine clinical practice. (J Am Coll Cardiol Img 2015;■:■-■) © 2015 by the American College of Cardiology Foundation.

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**ABBREVIATIONS
AND ACRONYMS****BMPR2** = bone morphogenetic protein receptor type II**CTEPH** = chronic thromboembolic pulmonary hypertension**CMR** = cardiac magnetic resonance**CO** = cardiac output**EF** = ejection fraction**ExCMR_{ip}** = exercise cardiac magnetic resonance imaging with simultaneous invasive pressure registration**mPAP** = mean pulmonary artery pressure**PAP** = pulmonary artery pressure**PEA** = pulmonary endarterectomy**ROC** = receiver-operating characteristic**RV** = right ventricular**RVESPV_R** = right ventricular end-systolic pressure-volume ratio**RVESPA_R** = right ventricular end-systolic pressure-area ratio**sPAP** = systolic pulmonary artery pressure**SV** = stroke volume

There is broad agreement that exercise-induced pulmonary hypertension is an important clinical finding with diagnostic and prognostic utility in a broad range of cardiac and pulmonary vascular conditions (1). Echocardiography remains the primary screening tool for pulmonary vascular disease. However, echocardiographic estimation of pulmonary artery pressure (PAP) during exercise is not routine because of concerns regarding the imprecision and lack of standardization of exercise measures (2,3).

Recent studies demonstrated a consistent nearly linear relationship between changes in PAP and cardiac output (CO) (1,4-6) with an expected increase in mean pulmonary artery pressure (mPAP) of ~1 to 2 mm Hg/l/min of CO representing a normal pulmonary vascular response and any value greater than 3 mm Hg/l/min being suggestive of pathology (1). This represents a more physiological appraisal than single peak exercise measures as the flow-dependent characteristics of the circulation are encompassed in the separation of normal from abnormal. Although the advantages of an approach incorporating PAP in relation to CO or exercise intensity are now well accepted, the accuracy and precision of noninvasive estimates of these relationships remain to be proved against gold standard measures.

We sought to validate echocardiographic measures of PAP and CO during intense exercise compared with the reference standards of invasive PAP and exercise cardiac magnetic resonance (CMR), having previously validated this against direct Fick measurements of CO (7). Thus, echocardiographic measures were compared with those from a hybrid invasive CMR technique in healthy subjects and patients with pulmonary vascular pathology. Furthermore, the use of CMR as a gold standard for right ventricular (RV) measures enables us to simultaneously validate echocardiographic measures of RV functional reserve.

METHODS

SUBJECTS. Sixty-one subjects underwent evaluation with exercise echocardiography and exercise CMR imaging combined with invasive PAP estimates (subsequently referred to as exercise cardiac magnetic resonance imaging with simultaneous invasive pressure registration [ExCMR_{ip}]) within a 24-h time-frame. The study population comprised a range of healthy subjects and patients with pulmonary vascular disease including 19 endurance athletes, 9 healthy nonathletes, 8 asymptomatic carriers of a mutation linked to the development of pulmonary arterial hypertension (BMPR2 [bone morphogenetic protein receptor type II] mutation), 5 subjects with persisting exertional dyspnea after pulmonary embolism, 14 patients with chronic thromboembolic pulmonary hypertension (CTEPH), and 6 patients undergoing routine hemodynamic evaluation 6 months after pulmonary endarterectomy (post-PEA).

STUDY DESIGN. Cardiopulmonary exercise testing was performed on an upright cycle ergometer to determine maximal exercise power. On the same day, echocardiography was performed with subjects at both rest and during incremental exercise at 25%, 50%, and 66% of maximal upright exercise power, as previously described (7,8).

Within 24 h after exercise echocardiography, all subjects underwent exercise ExCMR_{ip} at the same workloads as for the echocardiography protocol. Before exercise, a 7-F pulmonary artery catheter was inserted in the internal jugular vein and guided under fluoroscopy to the proximal right main pulmonary artery. In the CMR suite, these catheters were attached to CMR-compatible pressure transducers that were connected to a PowerLab recording system (AD Instruments, Oxford, United Kingdom). Pressure measurements were continuously recorded during the exercise CMR protocol and analyzed off-line using LabChart v6.1.1 (AD Instruments). All pressure measurements were averaged over 10 consecutive cardiac cycles during unrestricted respiration (1).

ECHOCARDIOGRAPHY. Resting and exercise echocardiography was performed on a semisupine cycle

trials by different manufactures of cardiac implantable electronic devices (Medtronic, Boston Scientific, Biotronik, St. Jude Medical, and Sorin). Dr. La Gerche is funded by a Career Development Fellowship from the National Health and Medical Research Council and National Heart Foundation of Australia (NHMRC and NHF). Dr. Schnell is funded by a grant from the French Federation of Cardiology. Dr. Heidbuchel is on the Speakers Bureau and Advisory Board of Bayer, Boehringer-Ingelheim, Daiichi Sankyo, Bristol-Myers Squibb, Pfizer, Merck, Biotronik, and St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The first 2 authors contributed equally to this work.

Manuscript received April 17, 2015; revised manuscript received June 9, 2015; accepted June 18, 2015.

ergometer (Easystress, Ecogito Medical sprl, Liege, Belgium). Images were acquired using a Vivid E9 ultrasound system (GE Vingmed Ultrasound AS, Horten, Norway) and analyzed off-line using EchoPAC version 112 (GE Vingmed Ultrasound AS).

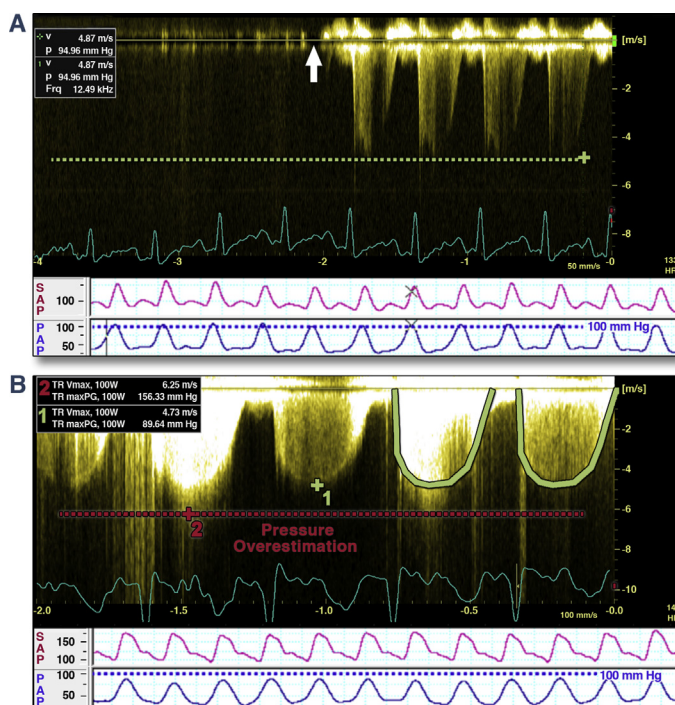
Both at rest and during exercise, systolic pulmonary artery pressure (sPAP) was estimated from the maximal transtricuspid regurgitant velocities with colloid contrast enhancement (**Figure 1**), without the addition of right atrial pressure estimates (4,9), as previous investigations failed to demonstrate reliable accuracy, and no studies have validated estimates during exercise (10). mPAP was estimated from sPAP measurements using the Chemla formula: $mPAP = 0.61 \times sPAP + 2$ (11). CO was derived from the Doppler-estimated stroke volume (SV) using the velocity time integral of flow through the left ventricular outflow tract (5). RV fractional area change (**Figure 2A**) and tricuspid annular plane systolic excursion were calculated from a single-plane 4-chamber view as described previously (9). The right ventricular end-systolic pressure-area ratio (RVESPAR), a surrogate of RV contractility, was calculated as sPAP divided by RV end-systolic area (9). The ratio of peak exercise RVESPAR divided by resting RVESPAR was calculated as a surrogate of RV contractile reserve.

CMR EQUIPMENT, IMAGE ACQUISITION, AND ANALYSIS. Biventricular volumes were measured during supine cycling exercise using a real-time CMR method that we previously validated against invasive standards (7). In brief, subjects performed supine exercise within the CMR bore using a cycle ergometer with adjustable electronic resistance (Lode, Groningen, the Netherlands). Images were acquired with a Philips Achieva 1.5-T CMR with a 5-element phased-array coil (Philips Medical Systems, Best, the Netherlands).

Using an in-house-developed software program (RightVol, Leuven, Belgium), left ventricular and RV end-diastolic volume, end-systolic volume, and SV were calculated by a summation of disks (**Figure 2B**). CO was measured as the product of SV and heart rate, whereas ejection fraction (EF) was calculated as SV/end-diastolic volume. Similar to RVESPAR, the ExCMR_{ip}-derived RVESPV was calculated as sPAP/RV end-systolic volume, whereas the ratio of peak exercise to resting RVESPV was used to estimate RV contractile reserve.

STATISTICAL ANALYSIS. Data were analyzed using SPSS version 22 software (IBM, Chicago, Illinois). Gaussian distribution of all continuous variables was tested using a Kolmogorov-Smirnov test. Descriptive data for continuous variables are presented as mean

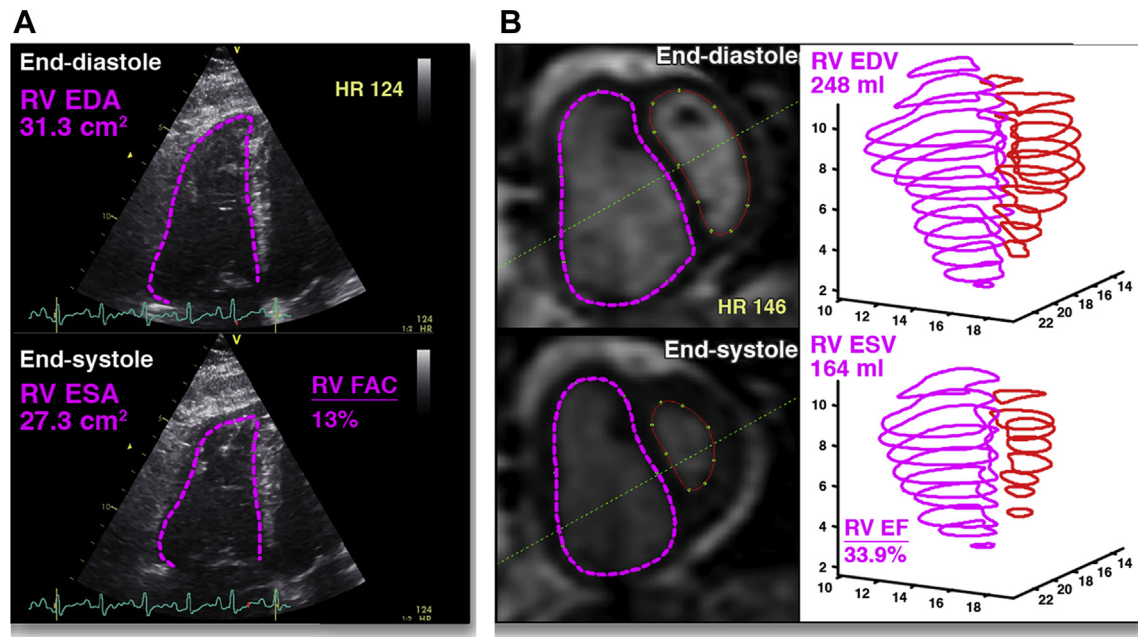
FIGURE 1 PAP Measurement Using Colloid Enhancement of the Tricuspid Regurgitation Signal



(A) Administration of agitated colloid enhancement (**white arrow**) enables pressure estimation during exercise in a patient in whom no tricuspid regurgitant signal could be obtained without contrast. The **dotted green line** depicts the estimation of systolic pulmonary artery pressure (sPAP) by echocardiography, whereas systemic artery pressure (SAP) and pulmonary artery pressure (PAP) denote invasive SAP and PAP measurements. (B) Potential for significant pressure overestimation (**red dotted line and marker**) because of noisy signal artifacts related to contrast enhancement. Careful measurement of only the enhanced signal with a shape similar to the normal tricuspid regurgitation flow velocity profile (**green curve**) yields sPAP values similar to those derived invasively.

± SD or as median (25% and 75% percentiles) where appropriate. Categorical data were compared using the Fisher exact test.

The relationships between individual PAP, CO, and workload were determined using linear regression analysis (8). A Bland-Altman analysis was used to assess the accuracy and precision of echocardiography-derived hemodynamics compared with ExCMR_{ip} (12). The bias, SD, and 95% limits of agreement were reported. Receiver-operating characteristic (ROC) curves were constructed to determine the diagnostic accuracy of echocardiography-derived pulmonary vascular pressure/flow and pressure/workload relationships to detect an abnormal pulmonary vascular reserve, defined as an mPAP-CO slope >3 mm Hg/l/min by ExCMR_{ip}. Similarly, ROC curves were constructed to assess the diagnostic

FIGURE 2 Assessment of RV Function During Exercise by Echocardiography and ExCMR_{ip}

End-diastolic and end-systolic image frames are depicted at peak exercise in a patient with impaired right ventricular (RV) functional reserve due to chronic thromboembolic pulmonary hypertension. From these images, RV fractional area change (FAC) is calculated using echocardiography (A), whereas a summation of disks is used to calculate RV ejection fraction (EF) by ExCMR_{ip} (B). See [Online Video 1](#). EDA = end-diastolic area; EDV = end-systolic volume; ESA = end-systolic area; ESV = end-systolic volume; ExCMR_{ip} = exercise cardiac magnetic resonance imaging with simultaneous invasive pressure registration; HR = heart rate.

accuracy of RVESPAR to identify CTEPH and post-PEA patients in whom RV contractile reserve during exercise is impaired (8). Diagnostic accuracy was quantified by the area under the ROC curve.

The impact of exercise on the sPAP-mPAP relationship was evaluated by a linear mixed model that included sPAP, condition (rest vs. peak exercise), and their interaction as fixed effects. To account for the repeated nature of the data, an unstructured variance-covariance matrix was included in the model. A *p* value <0.05 was considered statistically significant.

RESULTS

The clinical characteristics of the 61 subjects are summarized in [Table 1](#).

ASSESSMENT OF PAP BY ECHOCARDIOGRAPHY VERSUS INVASIVE MEASURES. At rest, echocardiographic measures of sPAP were possible in 57 of 61 subjects (93%). The number of subjects in whom a Doppler echocardiographic estimate of sPAP could be obtained decreased to 46 (75%), 49 (80%), and

42 (69%) for low-, moderate- and peak-intensity exercise, respectively.

At rest, an excellent correlation was found between echocardiographic and invasive measures, for both sPAP and mPAP ([Figure 3A](#)). No significant bias was observed for echocardiographic estimation relative to invasive sPAP, whereas mPAP calculated from echocardiography-derived sPAP using the Chemla formula were higher than invasively measured mPAP ([Table 2](#)). The difference in sPAP was <10 mm Hg in 41 of 57 subjects (72%) and >20 mm Hg in 5 subjects (9%). Similarly, for mPAP, the difference was <10 mm Hg in 47 subjects (83%) and >20 mm Hg in 1 subject (2%).

At peak exercise, echocardiography-derived sPAP and mPAP correlated strongly with invasive measures ([Figure 3A](#)). There was no significant bias between invasive and echocardiographic measures of sPAP at peak exercise, whereas echocardiography overestimated mPAP ([Table 2](#)). The difference in peak exercise invasive and echocardiography-derived sPAP was <10 mm Hg in 20 of 42 subjects (48%) and >20 mm Hg in 4 subjects (10%).

Considering all workloads, echocardiographic estimates of mPAP were higher than those measured invasively ($+5.1 \pm 6.9$ mm Hg; $p < 0.0001$), whereas the bias in sPAP was not statistically significant (mean bias $+1.6 \pm 11.6$ mm Hg; $p = 0.055$). The bias in mPAP remained significant when CTEPH and post-PEA patients were excluded (mean bias $+4.9 \pm 6.7$ mm Hg; $p < 0.0001$). Analysis of the relationship between invasive sPAP and mPAP revealed an excellent linear correlation ($\text{mPAP} = 0.54 \times \text{sPAP} + 1.9$, $R^2 = 0.96$; $p < 0.0001$). When the values at each exercise intensity were considered separately, the relationship between invasive sPAP and mPAP was very similar (Online Table 1), indicating consistency of the relationship throughout exercise. Using the regression equation derived from our data ($\text{mPAP} = 0.54 \times \text{sPAP} + 1.9$) in preference to the Chemla formula, there was only minimal bias between echocardiography and ExCMR_{ip} measures of mPAP ($+1.3 \pm 6.7$ mm Hg; $p = 0.008$) with 95% limits of agreement of -11.8 to 14.4 mm Hg. Estimation of sPAP by echocardiography did not include addition of right atrial pressure such that sPAP measurements by echocardiography equaled invasively derived sPAP minus right atrial pressure. When this formula was used to compare echocardiographic and invasive measurements, a small but consistent bias was seen (Online Figure 1), demonstrating that some of the inaccuracy between echocardiography and invasive measurements was due to exercise-induced increases in right atrial pressure in the pulmonary hypertension patients.

ASSESSMENT OF PULMONARY VASCULAR RESERVE.

At rest, CO measured by echocardiography was significantly lower than values using ExCMR_{ip} due to underestimation of SV (Table 2, Figure 3B). The difference in SV remained similar from rest to peak exercise, whereas the difference in CO increased because peak exercise heart rate was lower during exercise echocardiography (141 ± 24 beats/min vs. 124 ± 19 beats/min; $p < 0.0001$).

One healthy subject (4%), 1 BMPR2 carrier (13%), 3 post-pulmonary embolism patients (60%), 12 CTEPH patients (86%), and 6 post-PEA patients (100%) had abnormal pulmonary vascular reserve as defined by the mPAP/CO cutoff of >3 mm Hg/l/min by ExCMR_{ip} (Online Figure 2). Multipoint PAP/CO slope determination by echocardiography was possible in 53 of 61 subjects (87%), whereas the success rate in obtaining peak exercise PAP measurements alone was 69% ($p = 0.028$). As depicted in Figure 4, echocardiography had good accuracy and precision for the assessment of individual mPAP/CO slopes. For the detection of the presence of abnormal pulmonary vascular reserve, the area under the ROC curve was 0.88 (95%

TABLE 1 Clinical Characteristics

Age, yrs	46 (32, 57)
Male	46 (75)
Height, cm	175 ± 12
Weight, kg	79 ± 14
BMI, kg/m ²	26.1 ± 4.8
Subjects	
Endurance athletes	19
Healthy nonathletes	9
BMPR2 mutation carriers	8
Post-PE patients	5
CTEPH patients	14
Post-PEA patients	6

Values are median (25th, 75th percentile), n (%), or mean \pm SD.

BMI = body mass index; BMPR2 = bone morphogenetic protein receptor type II; CTEPH = chronic thromboembolic pulmonary hypertension; PE = pulmonary embolism; PEA = pulmonary endarterectomy.

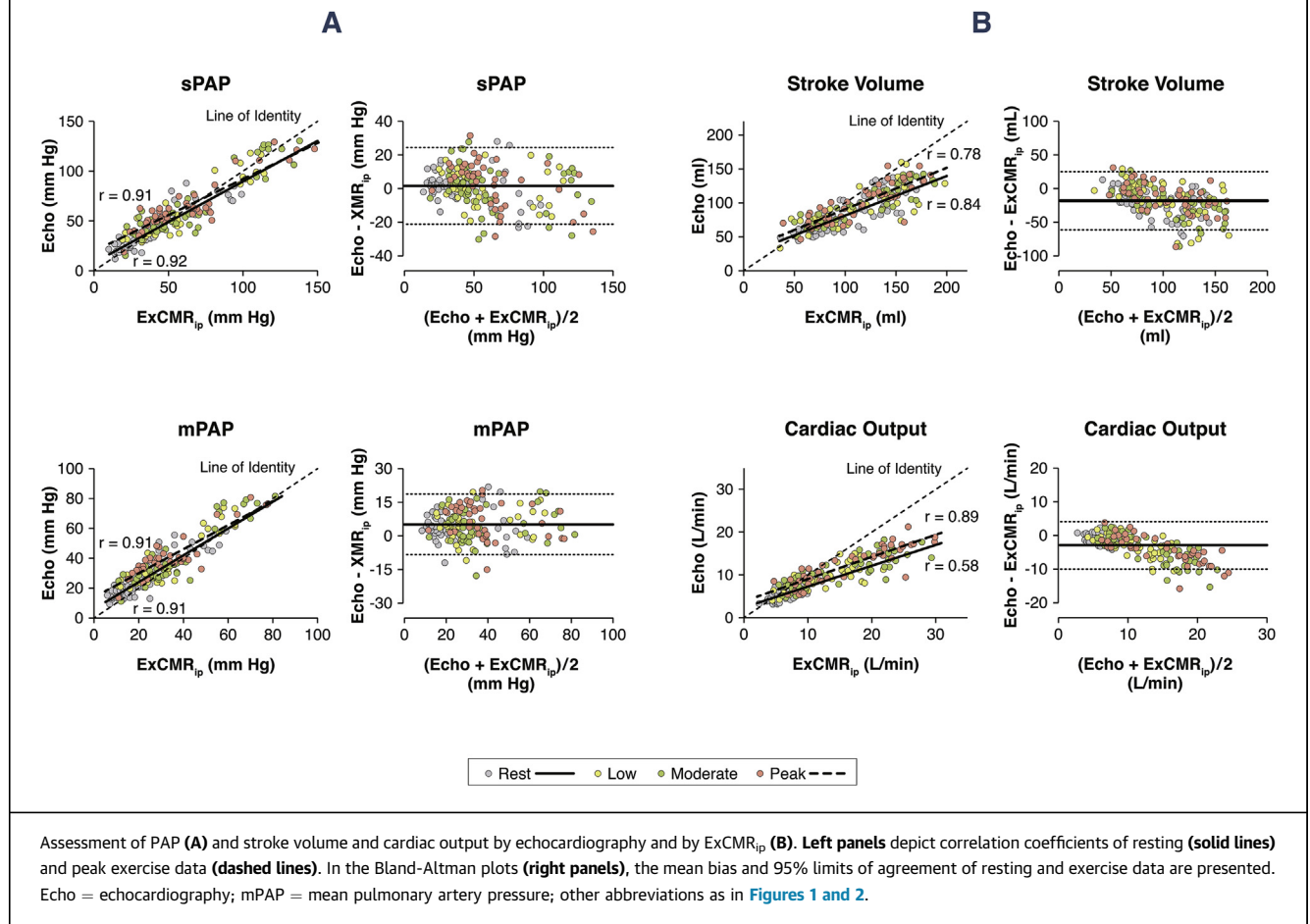
confidence interval [CI]: 0.77 to 1.00; $p < 0.0001$), and mPAP/CO by echocardiography of 3.2 mm Hg/l/min was identified as the most favorable threshold, with 88% sensitivity and 81% specificity.

We also evaluated the use of simplified relationships by plotting sPAP against CO and exercise intensity in Watts. As shown by Online Figure 3, we found a consistent linear relationship between CO and exercise intensity with limited interindividual variability ($\text{CO} = 0.07 \times \text{power [in Watts]} + 6.8$). ExCMR_{ip}-derived mPAP/CO slopes correlated strongly with echocardiography-derived sPAP/W and sPAP/CO slopes (Figure 4). ROC analysis showed that cutoff values of >0.47 mm Hg/W for sPAP/W and >5.2 mm Hg/l/min for sPAP/CO slopes had a sensitivity of 86% and 88% and a specificity of 94% and 81% to depict abnormal pulmonary vascular reserve (area under the curve, 0.95 [95% CI: 0.88 to 1.01] and 0.88 [95% CI: 0.77 to 1.0], respectively; $p < 0.0001$).

EVALUATION OF RV CONTRACTILE RESERVE. The number of patients in whom tricuspid annular plane systolic excursion and RV fractional area change could be obtained decreased from 60 (98%) and 57 (93%) at rest to 53 (87%) and 50 (82%) at peak exercise, respectively.

At both rest and peak exercise, the correlation between RVEF and RV fractional area change was higher than that between RVEF and tricuspid annular plane systolic excursion (Figure 5). An example of exercise echocardiography and ExCMR_{ip} for the assessment of RV functional reserve in a CTEPH patient is provided in Figure 2 and Online Video 1.

The association between RVESPAR and RVESFVR was strong at rest and moderate at peak exercise (Figure 5). Overall, an excellent correlation was found when either sPAP or mPAP was used to calculate

FIGURE 3 Assessment of PAP, Stroke Volume, and Cardiac Output

RVESPV (R² = 0.86; p < 0.0001). The correlation remained excellent when only CTEPH and post-PEA patients were considered (R² = 0.89). The ratio of peak exercise to resting RVESPV correlated moderately with the ratio of peak exercise to resting RVESPV (Figure 5). At rest, CTEPH and post-PEA patients had higher RVESPV and RVESPV compared with the other groups (0.73 ± 0.24 mm Hg/ml vs. 0.32 ± 0.23 mm Hg/ml and 3.56 ± 1.05 mm Hg/cm² vs. 2.31 ± 1.27 mm Hg/cm²; p < 0.01). However, the ratios of peak exercise to resting RVESPV and RVESPV were significantly reduced in CTEPH and post-PEA patients (1.45 ± 0.30 vs. 3.30 ± 1.09 and 1.45 ± 0.38 vs. 2.84 ± 1.24 ; both p < 0.01), indicating that the exercise-induced increase in RV contractility was impaired. The RVESPV ratio of 2.01 from rest to peak exercise had a sensitivity and a specificity for identifying CTEPH and post-PEA patients of 100% and 98% (AUC 0.99 [95% CI: 0.98 to 1.00]), respectively, whereas a peak exercise to resting RVESPV ratio of

1.64 had a respective sensitivity and specificity of 82% and 96% (AUC 0.94 [95% CI: 0.87 to 1.02]) (Figure 6).

DISCUSSION

We demonstrate that measures obtained during exercise echocardiography can provide a sufficiently robust estimate of PAP changes during exercise and CO to justify inclusion in daily clinical practice as a means of identifying abnormalities in pulmonary vascular function. Determination of PAP/CO slopes by echocardiography was feasible in the majority of subjects and had good accuracy for identifying abnormal vascular reserve. Furthermore, simplified relationships between sPAP and exercise intensity measured in Watts can also be used to identify pathology and may represent a simpler clinical tool by avoiding the need for CO quantification. Finally, this is the first study to validate echocardiographic

TABLE 2 Assessment of Pulmonary Arterial Pressures, Cardiac Output and Pressure/Flow and Pressure/Workload Relationships by Echocardiography Versus Combined CMR/Invasive Measures

	ExCMR _p	Echocardiography	Bias	p Value of Bias	SD of Difference	Limits of Agreement
sPAP, mm Hg						
Rest	36.1 ± 25.9	37.7 ± 22.9	1.7	0.21	10.0	−17.9 to 21.2
Peak exercise	61.9 ± 31.4	64.8 ± 25.1	2.9	0.17	13.6	−23.7 to 29.6
mPAP, mm Hg						
Rest	21.0 ± 14.2	25.0 ± 14.0	4.1	<0.0001	6.1	−7.9 to 16.0
Peak exercise	34.2 ± 17.2	41.5 ± 15.3	7.3	<0.0001	7.4	−7.1 to 21.7
CO, l/min						
Rest	6.5 ± 1.8	5.5 ± 1.5	−1.0	<0.0001	1.6	−4.0 to 2.1
Peak exercise	16.6 ± 7.2	12.4 ± 4.3	−4.2	<0.0001	4.0	−12.0 to 3.7
SV, ml						
Rest	98.0 ± 32.7	80.4 ± 24.5	−17.6	<0.0001	20.6	−58.1 to 23.0
Peak exercise	114.9 ± 38.7	100.0 ± 28.0	−15.0	<0.0001	21.5	−57.2 to 27.2
mPAP/CO, mm Hg/l/min	3.3 ± 3.6	4.1 ± 3.8	0.90	0.007	2.3	−3.6 to 5.4
sPAP/CO, mm Hg/l/min	5.9 ± 6.4	6.8 ± 6.2	−0.85	0.18	4.6	−8.1 to 9.8
sPAP/W, mm Hg	0.42 ± 0.40	0.42 ± 0.37	0.001	0.99	0.24	−0.47 to 0.47

Values are mean ± SD.

CMR = cardiac magnetic resonance; CO = cardiac output; ExCMR_p = exercise cardiac magnetic resonance imaging combined with invasive pulmonary artery pressure estimates; mPAP = mean pulmonary artery pressure; mPAP/CO = mean pulmonary artery to cardiac output slope; sPAP = systolic pulmonary artery pressure; sPAP/CO = systolic pulmonary artery pressure to cardiac output slope; sPAP/W = systolic pulmonary artery pressure to workload (in Watts) slope; SV = stroke volume.

measures of RV function during exercise against a reference standard.

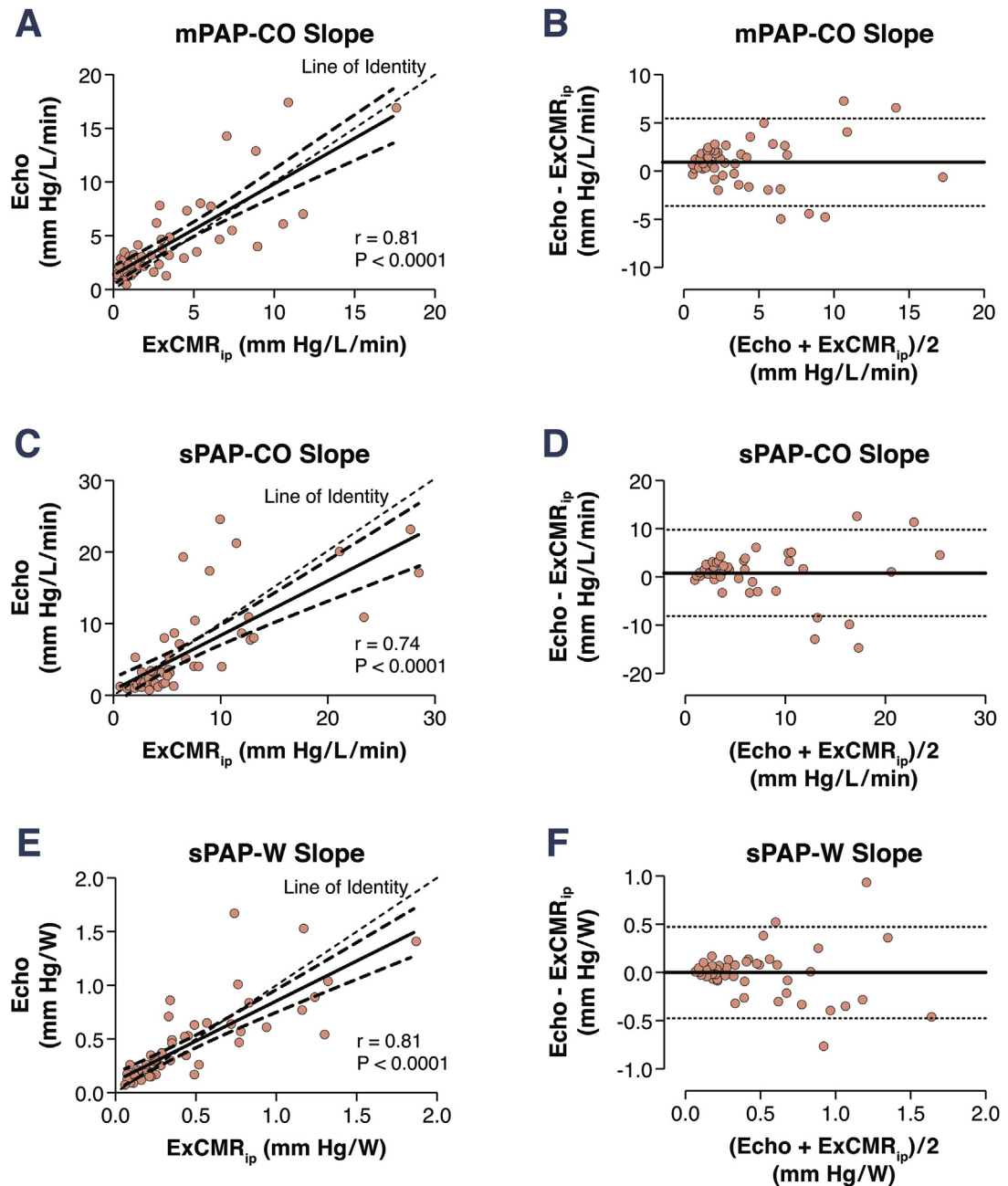
ACCURACY OF PAP ESTIMATION USING EXERCISE ECHOCARDIOGRAPHY. Despite its role as the primary screening tool to detect pulmonary hypertension, the feasibility and robustness of Doppler echocardiography to accurately assess sPAP has been questioned, particularly during exercise (2,13). Compared with previous studies, we found a significantly higher feasibility of PAP estimation by echocardiography, which is likely explained by the use of colloid-agitated contrast enhancement (13,14). Moreover, the use of multipoint exercise measurements enabled PAP/CO slope determination in 87% of subjects, even when PAP could not be determined at peak intensity exercise. This technique has significant advantages over the more commonly used method of comparing rest values with a single “peak exercise” value obtained when imaging constraints are greatest.

The use of agitated contrast enhancement may also explain the higher precision of sPAP estimates compared with some previous studies (2,15), although there was a tendency to overestimate sPAP, which may also be a consequence of contrast enhancement due to broadening of the spectral Doppler signal (14). Some of this “overestimation” may also be due to the fact that sPAP was generally estimated from the highest tricuspid regurgitant velocity signals, whereas the invasive measurement of sPAP was

recorded as the average of maximal values. This averaging can lead to significantly lower values, especially during exercise when the respiratory variation in sPAP is considerable.

Interestingly, although there was no significant bias between invasive sPAP and echocardiographic estimates, invasive mPAP values were significantly lower than echocardiographic estimates. mPAP is not measured directly using echocardiography, and, thus, accuracy is dependent on extrapolation from sPAP conversions. When we used the regression equation from our own invasive data, we found that much of the overestimation of echocardiography-derived mPAP was in fact due to a slightly different regression equation in our cohort compared with the Chemla formula. We cannot exclude that the different regression equation in our study is explained by the use of fluid-filled catheters as opposed to high-fidelity micromanometers in the study by Chemla et al. (11). Also, the inclusion of CTEPH patients (with and without PEA) may have influenced the relationship between sPAP and mPAP (16), even though exclusion of these patients did not alter our results.

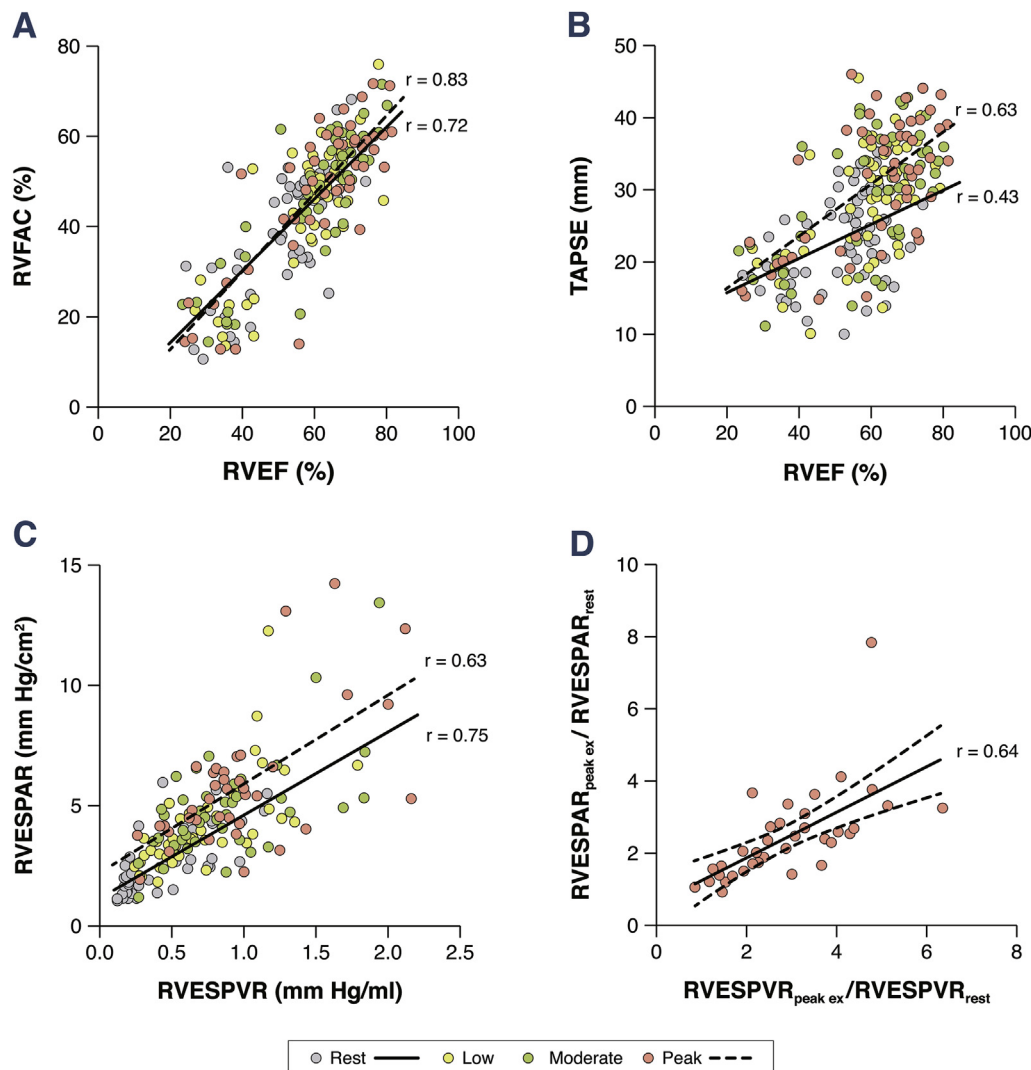
PULMONARY VASCULAR PRESSURE/FLOW AND PRESSURE/WORKLOAD RELATIONSHIPS. When differentiating a normal from an abnormal pulmonary vascular response to exercise, it is important to interpret changes in PAP against CO or workload (4). Noninvasive and invasive studies have suggested that

FIGURE 4 Comparison of Pulmonary Vascular Pressure/Flow and Pressure/Workload Relationships by Echocardiography and ExCMR_{ip}

Correlation coefficients with 95% confidence intervals (**A** through **C**) and Bland-Altman plots (**B** through **F**) of the slopes of mean PAP to CO (mPAP/CO slopes) (**A**), of systolic pulmonary artery pressure to cardiac output (sPAP/CO slopes) (**B**), and sPAP to workload in Watts (sPAP/W slopes) (**C**). CO = cardiac output; other abbreviations as in [Figures 2 and 3](#).

the slope of mPAP/CO ranges should not exceed 3.0 mm Hg/l/min in healthy subjects (1). We found that mPAP/CO slopes obtained with echocardiography were consistently higher than those obtained with

ExCMR_{ip}. This resulted from both overestimation of mPAP, on the one hand, and underestimation of CO, on the other, particularly at peak exercise intensity. Nevertheless, the echocardiography-derived mPAP/CO

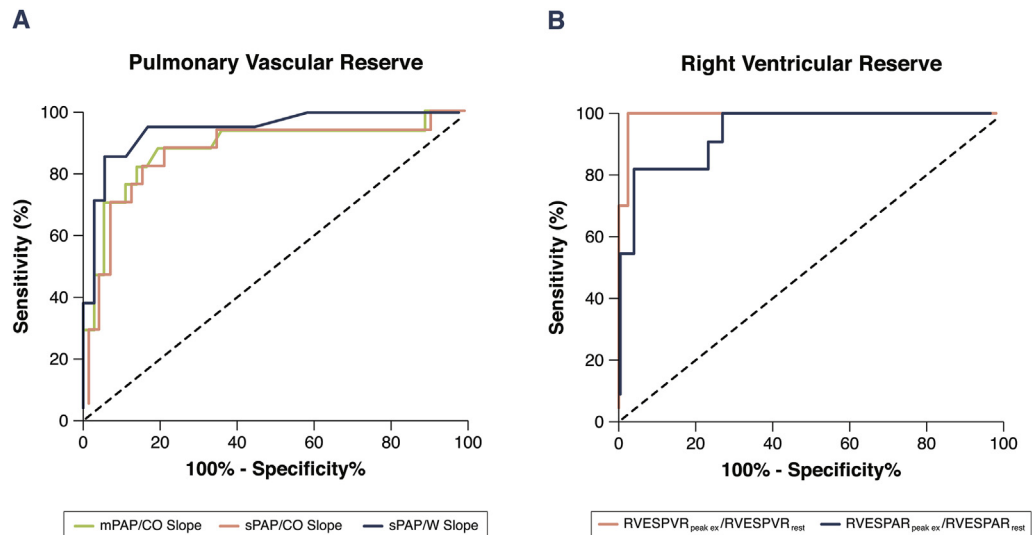
FIGURE 5 Measurement of RV Functional Reserve by Echocardiography and ExCMR_{ip}

Correlations between RVEF and right ventricular fractional area change (RVFAC) (A) and tricuspid annular plane systolic excursion (TAPSE) (B), respectively, at both rest (solid lines) and peak exercise (dashed lines). (C) Relationship between resting (solid line) and peak exercise (dashed line) right ventricular end-systolic pressure/volume ratio (RVESPVR) by ExCMR_{ip} and right ventricular end-systolic pressure/area ratio (RVESPAR) by echocardiography. (D) Correlation, with 95% confidence intervals, of the ratios of peak exercise with resting RVESPVR and RVESPAR. Abbreviations as in Figures 2 and 3.

slope predicted an abnormal pulmonary vascular response in the majority of subjects in whom ExCMR_{ip} values were abnormal. Even better accuracy was found for the slopes of sPAP to exercise intensity in Watts rather than CO. In general, determination of PAP to CO is preferred over workload because the main determinant of PAP is flow (1). However, despite the marked interindividual variability of CO at any given workload, our data demonstrate that the increase in CO relative to the increase in workload is in

fact very similar among all study subjects. Moreover, we demonstrate that the sPAP-to-workload relationship can be used to identify pathology. This may be a simpler and more pragmatic approach to include evaluation of pulmonary vascular reserve in clinical practice by avoiding the need for CO quantification.

RV FUNCTIONAL RESERVE. Although some studies have analyzed pulmonary vascular responses to exercise, there are very few data assessing changes in RV function during exercise. Exercise CMR has

FIGURE 6 Accuracy of Echocardiography to Assess Pulmonary Vascular and RV Reserve

(A) Receiver-operating characteristic curves for echocardiographic pulmonary vascular pressure/flow and pressure/workload relationships. Simplified relationships between sPAP and exercise intensity have similar accuracy compared with echocardiography-derived sPAP and mPAP/CO slopes to identify abnormal pulmonary vascular reserve. (B) Receiver-operating characteristic curves for right ventricular end-systolic pressure/volume and pressure/area relationships to identify patients with impaired right ventricular contractile reserve. Abbreviations as in Figures 3 to 5.

emerged as a promising technique enabling accurate and reproducible quantification of biventricular volumes during strenuous exercise (7). However, although exercise CMR offers superb insights into the mechanics and quantification of impaired cardiac reserve, simpler tests are needed for clinical practice.

In this study, we found a good correlation between echocardiographic measurement of exercise-induced RV dimensional changes, such as RV fractional area change and tricuspid annular plane systolic excursion, and RVEF obtained by ExCMR_{ip}. However, due to the influence of load on these measures, they tend to reflect right ventricular-arterial coupling rather than measures of RV contractility per se (9). To distinguish between RV dysfunction and/or pathological increases in pulmonary vascular load, we combined sPAP and RV end-systolic area using echocardiography to calculate RVESPAR as a surrogate of RV contractility (9). Our current results show that exercise-induced increases in RVESPAR correlate strongly with increases in RVESPVR obtained by ExCMR_{ip}. Recent data from our group indicated that CTEPH and post-PEA patients have higher RV contractility at rest compared with healthy subjects to compensate for increases in RV afterload (8). However, the right ventricle's ability to further increase contractility with exercise is diminished in these

patients, resulting in an uncoupling of RV contractility and pulmonary arterial load (8). Resting RVESPVR and RVESPAR are higher in CTEPH patients, whereas the ratios of peak exercise to resting RVESPVR and RVESPAR are significantly reduced. Therefore, the ratio of peak exercise to resting RVESPAR may be a promising noninvasive index of RV contractile reserve. It has been shown for the left ventricle that the end-systolic pressure-volume ratio response to exercise using echocardiography predicts clinical outcome and provides additional information beyond ejection fraction (17,18). The same approach, however, remains to be tested for the right ventricle.

STUDY LIMITATIONS. There are several potential limitations to our study. First, the subject population consisted of a mixture of various diagnostic groups that may not reflect the population in a clinical setting and may have artificially improved correlations among measures. Second, the exercise ExCMR_{ip} and exercise echocardiography tests cannot be performed simultaneously because of technical considerations. Furthermore, because the study protocol consisted of several exercise tests, we thought that performing all the measurements on 1 day was not feasible. However, all subjects underwent the

ExCMR_{ip} protocol within 24 h after Doppler exercise echocardiography. The augmentation of heart rate with increasing exercise intensity was slightly lower during the exercise echocardiography protocol despite cycling at the same workloads. Although this resulted in differences in heart rate at each level, the effect on the pressure/output relationship should not have been affected. Some of the inaccuracy between echocardiographic and invasive measurement of PAP was due to the fact that we did not include right atrial pressure estimates by echocardiography. In an analysis of a subgroup who underwent invasive right atrial pressure measures during exercise, we demonstrated a tendency to underestimate sPAP by echocardiography in pulmonary hypertension patients in whom right atrial pressure increased during exercise. Thus, right atrial pressure cannot be assumed to remain constant throughout exercise. Furthermore, although multipoint PAP/CO slope determination was feasible in the majority of individuals, the success rate of obtaining PAP at peak exercise was significantly lower. Finally, end-systolic pressure was approximated as sPAP in all subjects. It has been demonstrated that end-systolic pressure varies according to the presence of pathology such that it approximates mPAP in normotensive subjects, whereas it is best estimated as sPAP with the development of pulmonary hypertension (19). However, as the purpose of the testing is to distinguish whether the exercise response is abnormal, an assumptive compromise is required. Nevertheless, because contractile reserve is derived as the change in RVESVPR or RVESPAR and given the constant relationship between sPAP and mPAP during exercise (20), the effect of these assumptions is minimized.

CONCLUSIONS

Echocardiography is a feasible and accurate tool for the evaluation of pulmonary vascular and RV

functional reserve during exercise in clinical practice. Simplified relationships between sPAP and exercise intensity in Watts can be used to identify pathology and may represent a simpler clinical tool by avoiding the need for CO quantification. Further studies are needed to determine the clinical relevance of these novel exercise parameters for identifying pulmonary vascular disease and RV dysfunction at an early stage.

ACKNOWLEDGMENTS The authors thank all the patients for participating in the study. They also thank Stefan Ghysels, Guido Putzeys, and Kris Byloos for their help in performing the exercise magnetic resonance imaging studies.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Echocardiography is a feasible, reproducible, and accurate tool for the evaluation of pulmonary vascular and RV functional reserve during exercise in clinical practice.

COMPETENCY IN PATIENT CARE AND PROCEDURAL

SKILLS: When evaluating pulmonary vascular reserve in clinical practice, simplified relationships between sPAP and exercise intensity can be used to identify pathology and represent a simpler clinical tool by avoiding the need for CO quantification.

TRANSLATIONAL OUTLOOK: These novel exercise parameters offer considerable potential for identifying clinically relevant pulmonary vascular disease and RV dysfunction at an early stage.

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KEY WORDS cardiac magnetic resonance imaging, echocardiography, exercise, pulmonary artery pressure, pulmonary hypertension, right ventricular function

 **APPENDIX** For the supplemental video and legends, and online table and figures, please see the online version of this article.